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COMPARING INTERVENTIONS FOR OPIOID DEPENDENT PATIENTS PRESENTING IN MEDICAL EDs

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**Dr. Rapp is the principal developer of Strengths-Based Case Management. He will provide training and ongoing supervision to the interventionists providing brief Strengths-Based Case Management to participants in this study, but will not directly perform any study-related procedures.*

SPECIFIC AIMS

We propose to investigate the effects of a promising brief treatment model on treatment initiation and engagement, substance use outcomes, and broader health outcomes for opioid dependent patients seen in a medical emergency department (ED) who are not currently engaged in treatment. The study will compare the effects of brief strengths-based case management (SBCM) to the effects of screening, assessment and referral alone (SAR). Participants will be screened and assessed in the ED using procedures based closely on those used in our recently-completed NIDA Clinical Trials Network trial of brief interventions for drug users presenting in EDs. Participants who report three or more opioid dependence criteria on the DSM-IV checklist will be randomly assigned (150 per group) to receive 1) up to 6 sessions of SBCM based on the model previously implemented by Rapp et al. (2008); or 2) SAR. Follow-up assessments will be completed at 3 and 6 months, by staff that is blinded to treatment condition.

Aims of the study are:

1. To identify the main effects of SBCM in mobilizing initiation of addiction treatment and engagement in pharmacotherapy for opioid dependence (in primary care or specialty care settings).
   - Hypothesis 1: SBCM will result in higher rates of initiation and engagement than SAR.

2. To identify the main effects of SBCM in reducing substance use.
   - Hypothesis 2: SBCM will result in greater reductions in opioid use than SAR.

3. To identify the main effects of SBCM on broader measures of health and life functioning.
   - Hypothesis 3: SBCM will result in greater improvement in quality of life related to psychological, social, environmental, and physical health domains than SAR.

4. To examine the interactions between treatment assignment and selected participant attributes in predicting treatment initiation, pharmacotherapy engagement, and substance use outcomes.
   - Hypothesis 4: SBCM will have a larger effect on initiation and engagement in participants with lower environmental stability at baseline.

5. To examine effects of treatment involvement on substance use outcomes.
   - Hypothesis 5: Treatment initiation and pharmacotherapy engagement will significantly mediate the effects of study interventions on substance use outcomes, accounting for the main effects of treatment assignment on opioid use.

RESEARCH STRATEGY

a. Significance

a.1. SUDs are highly prevalent among ED patients

High rates of psychoactive substance use have been found in EDs, with prevalences far exceeding community rates [1-3]. For example, one large US study reported estimates of current use among male and female ED patients of 21% and 13% for marijuana, 14% and 12% for opioids, and 4% and 10% for stimulants, respectively [2]. Among a group of 1,933 patients admitted into a hospital emergency department, 198 (10%) had a substance use disorder which contributed to the emergency department admission [3]. The prevalence of illicit drug use is substantially greater in EDs than in primary care settings [4]. Illicit drug use significantly complicates the initial diagnosis and medical management of the substance abusing patient [5]. Despite this, a relatively large percentage of such substance abusing patients are not referred to appropriate psychosocial services [1, 3]. The resources required to attend to these conditions places increased burden on the medical system, including considerable costs that are often not recovered [6]. As an example, individuals seen in EDs in Tennessee who were judged to have a substance use disorder (SUD) and for whom some form of treatment would be appropriate were much more likely to require hospitalization and had higher rates of previous ED utilization than those not having a SUD, accounting for an estimated US $777.2 million in extra hospital charges in 2000 dollars [1].

a.2. ED interventions for SUDs

In response to the impact and cost, both to individuals and health care delivery systems, there has been an increased focus on developing, implementing, and evaluating methods to identify and provide appropriate services to individuals having problematic substance use who are seen in EDs [1, 2, 6-12]. With regard to alcohol use disorders, several efficacy and effectiveness trials in ED settings have demonstrated that screening, brief interventions, and/or referral to specialized substance abuse treatment for those with alcohol use disorders and alcohol related problems can contribute to both subsequent reductions in alcohol consumption [13-18] and alcohol-related consequences [17, 19, 20]. However, other well-designed studies did not find significant intervention effects [21-25]. A 2008 meta-analysis reported that brief interventions reduced subsequent alcohol-related injury (OR = .59), but did not find a significant effect on drinking [26]. Another recent review focusing on brief alcohol interventions for injury patients in the ED noted that more intensive interventions tended to yield more favorable results, and that the heterogeneity of populations and interventions among these studies limit the strength of the conclusions that can be drawn [27].

Considerably less is known about the best methods of identifying and intervening with individuals using illicit drugs or abusing prescription medications. As opposed to dealing with hazardous or harmful drinking in ED settings, the evidence of the effectiveness of such interventions has been considered only suggestive for drug use disorders [11] and there has been a call for further research on the efficacy of screening and brief interventions for drug use, as well as the need to test the effectiveness of such interventions in real world settings [12]. In general, brief motivational interventions appear to be somewhat less effective with drug abusers than with alcohol-involved individuals with respect to engaging them into treatment [28, 29] or modifying their drug use [30-32]; what positive effects are obtained tend to deteriorate over time [33].

Among the CSAT-funded SBIRT sites [10], Washington State chose to implement its SBIRT program in EDs [34]. From its inception in 2003 through July 3, 2008, a total of 89,901 patients had received services through the 9 emergency departments participating in the WASBIRT project. Of these, 23.4% (21,074) screened positive and received an intervention and/or additional services for substance use. Over 2,000 patients, identified as either high or moderate drug use risk based on their screening scores, received either brief intervention or brief intervention followed by brief therapy or chemical dependency treatment, and were followed up at 6 months. Average days of drug use declined from 13.7 in the 30 days prior to the baseline assessment in the ED to 6.5 days in the 30 days prior to the 6-month follow-up. While a significant reduction in drug use was found in both high and moderate risk groups, the greatest reduction was seen in the high risk group, with more intensive treatment among the high-risk users associated with greater change. In addition to changes in substance use, Medicaid costs were reduced by $366 per member per month, and inpatient days were significantly reduced [35].

In spite of these encouraging results, randomized trials are necessary to draw inferences with confidence. Findings from a randomized trial of adolescent and young adult marijuana users in a pediatric ED

indicated that a brief intervention plus booster session resulted in higher rates of marijuana abstinence and reduced consumption compared to the assessment control condition [36]. We recently completed a multi-site trial (N = 1285) of an SBIRT intervention for drug users presenting in EDs through the NIDA CTN (CTN Protocol 0047) which was the first large randomized trial of an SBIRT intervention focused on adult drug users in EDs. Methods and rationale for this study have been described [37]. Briefly, the study included three conditions. The first control group received minimal screening only. A second group received much more intensive assessment and, if they met criteria for probable substance dependence, a referral to treatment. This group served as both an attention control and a minimal intervention. The third group received an intervention consisting of a 30 minute motivational enhancement therapy session conducted in the ED, followed by two telephone "booster" sessions of approximately 20 minutes. This 3-session intervention, an abbreviated form of Motivational Enhancement Therapy, could be considered either a very robust brief intervention or a very brief treatment. In spite of robust implementation of the interventions and excellent follow-up rates, no meaningful significant differences in outcome were found among the three treatment groups [38]. Furthermore, no significant treatment effects were found for clinically meaningful sub-groups defined by primary drug of abuse (cannabis, opioids, or cocaine), gender, ethnicity, or severity. These findings, combined with negative findings from recent large-scale trials of brief interventions for drug users conducted in primary care settings [39, 40], indicate that more intensive interventions may be required to benefit individuals with serious drug use disorders.

a.3. The treatment needs of opioid dependent patients are not met by brief interventions

Opioid dependence is a major public health problem which has grown due to the persistent elevation in prescription opioid misuse in the past decade [41, 42]. It seems clear that patients with moderate to severe opioid use disorder, a disorder which is severe and often chronic, are likely to benefit from more intensive treatment. Opioid dependence is different from other drug use disorders in that highly effective pharmacotherapies exist. Decades of research support the efficacy of methadone and other full agonists [43, 44]. Buprenorphine is well established as an effective partial agonist treatment [45, 46], and may be prescribed effectively in primary care settings [47, 48]. Both also reduce overdose deaths in comparison to drug-free treatment [49-51]. Although naltrexone in pill form has had only a small impact on treatment of opioid dependence, the depot formulation has been approved by the FDA for treatment of opioid dependence, and is another effective option that may be prescribed in medical settings [52, 53].

Brief interventions have limited effectiveness in getting drug dependent people to treatment. In an inner-city population of heroin and cocaine addicts receiving primary care, Bernstein et al. reported extremely low rates of addiction treatment involvement other than detoxification following brief intervention [54]. In an analysis of data from the SAMHSA-funded WASBIRT project in Washington State, Krupski et al. reported that patients receiving a brief intervention were somewhat more likely to engage in addiction treatment than propensity score-matched controls [55]. Overall, 33.8% of those receiving BI engaged in SUD treatment compared to 22.5% of controls. The effect of BI was less pronounced among those who had received prior SUD treatment. In a sample of substance users seeking treatment through a centralized intake unit, a single session intervention based on motivational interviewing did not significantly increase rates of linkage to treatment over standard of care (44.7% vs. 38.7%) [56]. One attractive alternative approach is to initiate buprenorphine treatment in the ED [57] (Currently being evaluated in R01DA025991, D'Onofrio PI). However, this requires both acceptance of this responsibility by the ED, and immediate access to follow-up outside of the ED. These conditions appear to limit the applicability of this model outside of academic settings.

a.4. Case Management is an effective method of linking dependent patients to definitive treatment

Case management has repeatedly been shown to be effective in improving treatment linkage and retention for substance abusers. Controlled trials of case management have included diverse substance abuse populations and settings, demonstrating improved linkage and retention among injection drug users and methadone maintenance programs [58-60], crack cocaine users and centralized intake units [56, 61], female welfare recipients [62], homeless substance abusers [63], dually diagnosed substance abusers [64], and crack cocaine users in aftercare treatment [65, 66]. In a large retrospective cohort study (N = 7,776) case managed clients were more likely to enter some form of on-going treatment following detoxification than non-case managed clients [67]. A recent meta-analysis co-authored by Collaborator Richard Rapp examined the case management literature relative to substance abusing populations and identified a mean effect size of d = .42

for linkage outcomes [68]. The effectiveness of case management in improving linkage and retention predicted improvements in outcomes such as reduced drug use and legal severity [65, 66].

SBCM, the case management model we propose to use (described in detail in Section c.8.2), has a particularly strong evidence base in populations relevant to the proposed trial. Both long-term and brief adaptations of SBCM have improved linkage and retention rates in a general population of substance abusers [69], opioid dependent drug users entering agonist treatment programs [59], and crack cocaine users participating in aftercare treatment [65, 66] and linking with substance abuse treatment [56]. In a study involving 678 patients with substance use disorders (68% cocaine or heroin) presenting at a centralized intake unit, those randomly assigned to 5 sessions of SBCM were more likely to link to treatment than those receiving motivational interviewing (55.0% vs. 44.7%, $p<.05$) or standard-of-care referral (55.0% vs. 38.7%, $p<.01$) [56].The brief model of SBCM also demonstrated positive outcomes in a multi-site CDC clinical trial in which five session SBCM was used to improve linkage with care among newly diagnosed HIV positive individuals [70]. Those receiving SBCM were significantly more likely than those who received passive referral to have had at least one HIV primary care visit in each of 2 consecutive 6-month follow-up periods. The sites from this controlled trial also participated in a follow-up implementation study to determine whether the model would be as effective when implemented by community HIV/AIDS organizations as it was in a closely monitored clinical trial [71]. The linkage rate across the ten sites was 79%, matching that of the controlled trial.

b. Innovation

As addiction treatment becomes increasingly integrated into the medical care system [72, 73], two models have rightly received a great deal of attention. The first is the use of SBIRT models to identify cases, provide therapeutic contact, and refer the more severe cases to longer-term care [9, 11, 74]. The second is the treatment of addictions using medical models of care, including those that can be implemented in primary care settings. Prime examples of the latter are buprenorphine [47, 75-78] and pharmacotherapies for alcohol dependence [79-82]. However, much less attention has been paid to optimizing strategies for bridging the gap between SBIRT and more intensive/longer-term treatment for those with more severe substance use disorders. This factor is of critical importance for opioid dependent patients, whose needs are not met by brief interventions or brief treatment, and for whom pharmacotherapy is often indicated.

Emergency room interventions for substance use disorders have been largely limited to brief interventions/SBIRT models, and these have focused primarily on alcohol. Although there is a substantial literature documenting the value of case management in linking drug users to treatment, this approach has not been applied to drug users in the ED setting. The proposed study will be the first to use a case management approach to link drug dependent patients presenting in EDs to longer-term addiction treatment. It will be one of the first trials focusing specifically on opioid dependent patients in medical EDs. A further innovative feature is that the case management approach will emphasize linkage to pharmacotherapy, facilitating linkage to office-based buprenorphine, methadone, or naltrexone for patients who desire these treatments.

c. Approach

c.1. Overview

We propose a 2-group design in which ED patients meeting criteria for opioid dependence are randomly assigned to receive up to 6 sessions of SBCM based on that used in prior trials [56, 70]; or Screening, Assessment, and Referral (SAR) without any on-site treatment. The initial SBCM session will take place as soon as possible following the participant's random assignment to the SBCM condition. If possible, this session will be completed before the participant leaves the ED, where patients have been successfully recruited for the now closed study: Screening, Motivational Assessment, Referral and Treatment in Emergency Departments (SMART-ED) (PI: Ryan McCormack, #i11-00298). Subsequent SBCM sessions will be conducted in the community or at Bellevue Hospital Center. Screening and assessment procedures will be similar to those used in the SMART-ED trial.

c.2. Participants

Participants will be adult men and women presenting for medical treatment in the ED.

c.2.1. Inclusion Criteria: 1) Registration as patient in the ED during study screening hours; 2) Endorsement of three or more opioid dependence criteria by self-report on the DSM-IV checklist; 3) Age 18 years or older; 4) Adequate English proficiency; 5) Ability to provide informed consent; 6) Self-report use of opioids in last 30 days.

c.2.2. Exclusion Criteria: 1) Inability to participate due to emergency treatment; 2) Significant impairment of cognition or judgment rendering the person incapable of informed consent. (e.g., traumatic brain injury, delirium, intoxication); 3) Status as a prisoner or in police custody at the time of screening; 4) Current engagement in substance use disorder treatment; 5) Inability to provide sufficient contact information (must provide at least 2 reliable locators); 6) Unavailable for follow-up (e.g., planning to relocate within 6 months); 7) Prior participation in the current study; 8) Current participation in a research study related to substance use.
c.2.3. Vulnerable Populations: Children will not be enrolled in the study. Pregnant women will be allowed to participate in the study. Because the interventions in this study are purely psychosocial (i.e., no medications are administered), the risks and benefits to pregnant women are not significantly different from those of other participants, so there is no justification for excluding them. No inducements, monetary or otherwise, will be offered to terminate a pregnancy. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate the pregnancy. Individuals engaged in the research will have no part in determining the viability of a neonate.

Prisoners will not be enrolled in the study. If a subject becomes incarcerated during the study, the individual may remain in the study and treatment and follow-up procedures may be continued in accordance with IRB and OHRP approvals. It is expected that approximately 10% of randomized participants will become incarcerated during the six months of their study participation. It is ethically problematic to exclude the vulnerable population since they have an even greater need for effective linkage to treatment than those without criminal justice involvement. It deprives this significant group of opioid addicted patients of possible benefits from evidence that this intervention could help them. Additionally, excluding prisoners compromises the scientific integrity of the study by causing a significant decrease in the follow-up rate. Based on other studies in similar populations, the overall follow up rate would be about 85% including prisoners, so without prisoners, closer to 75%. It's particularly problematic because the cases won't be missing at random. Allowance to extend the study intervention and substance use assessments to this population allows for continued engagement with treatment-focused research and continuity of case management. Participants in the SAR treatment group who become incarcerated will continue to participate in study activities which are considered to be above treatment-as-usual, including substance use assessments and referral to treatment. Consequences of discontinuation for SAR participants includes loss of these activities and information to which they would be otherwise entitled, all of which are considered to be beneficial to study participants. Participants in the SBCM treatment group who become incarcerated will participate in the same study activities as SAR participants and additionally engage in time-limited case management sessions. Consequences of discontinuation due to incarceration for participants in the SBCM group include loss of assessment, planning, linking, monitoring and advocacy provided by the case manager. Local standard operating procedures for the collection of prisoner data will be approved by the IRB. Data may be collected either in person, by phone, or in writing, provided that data collection follows the procedures approved by OHRP and the IRB. The research team will not share details of the nature of the research with staff at the jail/prison, or with parole or probation officers. Visits, whether in person or by phone, will only be conducted if the participant's confidentiality can be maintained and no audio-taping occurs. Incarcerated participants will be clearly informed in advance that participation in the research will have no effect on their probation or parole, nor will it confer any advantages or amenities beyond the potential benefits stated at the time of informed consent. Any possible advantages accruing to prisoners through participation in the research—when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the jail/prison—are not of sufficient magnitude as to impair prisoners' ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison.

c.3. Recruitment and screening
c.3.1. Recruitment. Participants will be recruited from the Bellevue Hospital Center ED, a large, urban, public-sector ED. The recruitment target for the proposed study is 2 participants per week.
c.3.2. Screening. Potential participants will be identified in two ways:

- Method 1) Patients with known opioid use will be referred to the study team by clinical ED staff. As part of an ongoing clinical (non-research) SBIRT program taking place in the Bellevue ED, ED staff screen and assess ED patients for unhealthy tobacco, alcohol, and drug use. ED staff will introduce patients who report illicit or non-medical use of opioids in the past year to study staff. Study RAs will then complete screening procedures (detailed below) with referred patients. This referral arrangement allows the ED staff to make the initial determination that the patient is

appropriate for potential study inclusion with regard to patient's medical stability and capacity to provide informed consent.

- Method 2) Study staff will introduce themselves to ED staff and inquire about patients who may be eligible to participate in the study. Study staff may approach ED patients directly only after ED staff has provided permission to do so.

The study RA will then request the patient's verbal consent, to complete the prescreen research assessment using an IRB-approved verbal consent script. After the patient has provided verbal (not signed) consent, the RA will collect anonymous information including English proficiency, age, gender, reason for ED visit, triage acuity level, non-prisoner status, days of opioid use in the past 30 days, and availability for treatment (See form entitled "Brief Information Tool") in order to determine potential eligibility and to collect data on representativeness of the study sample. These data will be collected by interviewing the patient, except for the triage level and reason for ED visit, which will be obtained from the "white board" (a patient tracking system which is visible to all staff working in the ED).

The RA will then administer the DSM-IV Checklist. Patients who meet DSM-IV criteria (endorsement of three or more opioid dependence criteria) will be further screened for eligibility using the Screening Instrument Secondary Screening Form. This form will provide a complete review of eligibility criteria. Those who are interested and eligible will then undergo the written informed consent process described in the Protection of Human Subjects section. Patients who screen out of the study will receive no further study intervention, but will receive the standard clinical intervention by ED staff as well as any patient education materials that are typically distributed after screening. Anonymous screening data will be kept to allow description of those who do not qualify. This is necessary to assess the representativeness of the included sample, and required by high quality medical journals.

Screening data will be collected by research personnel using direct entry into tablet computers to facilitate rapid screening, electronic data capture, and mobility within the busy ED setting. Refusals and inability to participate (e.g., unavailable due to emergency medical treatment, left without being seen) will be recorded. Study staff will time their intervention to minimize interference with medical treatment. Patients who show signs of intoxication (e.g., somnolence, slurring of speech) will not be screened unless and until these signs resolve.

c.4. Baseline Assessment

The baseline assessment for this trial will be kept considerably briefer than those traditionally used in addiction treatment trials. There are both methodological and practical reasons for this. It is important to keep the assessment battery brief in order to minimize assessment reactivity that can obscure treatment effects [83-87]. This is of particular concern for trials in which the dose of treatment is relatively small. The practical issue is that extensive assessments are likely to interfere with the rapid pace of clinical treatment in the ED setting. A cumbersome assessment process is also likely to impede the successful completion of the study through an adverse effect on recruitment and on the quality of the relationship between study staff and clinical ED staff. The baseline assessment will include an abbreviated Form-90 interview (described below) as the primary baseline measure of substance use. All consenting participants will also complete a demographic questionnaire, provide locator information, and provide a urine sample which will provide an objective measure of substance use, as well as the TCU-TMA, BTI, SIP-D, and WHOQoL Bref forms described in section c.10 below. None of the baseline assessments are clinical assessments. All study personnel will be trained in the administration of the assessments via formal protocol training. A Training Documentation Form, endorsed by the study's Principal Investigator, will certify the research team member's competence to complete the measures. The total time burden for the baseline assessment is approximately 100 minutes, comparable to that of the SMART-ED study (approximately 90 minutes). Participants who sign informed consent, complete the baseline assessment and meet all inclusion and exclusion criteria will proceed to randomization.

c.5. Randomization

Eligible participants will be randomly assigned in 1:1 ratio to (1) screening plus assessment and referral (SAR), (2) up to 6 sessions of strengths-based case management (SBCM). Randomization will follow a randomly permuted block randomization schedule set up within REDCap prior to beginning the trial, and allocation for each participant will be revealed only at the point of randomization. The RA will use a Randomization Form to document eligibility, treatment assignment, if randomized and, if not, the reason an eligible participant was not randomized. Once eligibility has been established, randomization will be performed and documented by

pushing the “Randomize” button on the Randomization form. There are a number of possible pre-treatment predictors of treatment engagement and opioid use outcomes, including age, gender, treatment history, addiction severity, psychosocial instability (e.g., housing), psychiatric comorbidity, and co-occurring other drug and alcohol use [88-91]. Studies are not consistent as to which factors are predictive, and existing studies may or may not be relevant to ED patients receiving SBCM. Therefore, randomization will not be stratified.

c.6. Follow-Up

Follow-up assessments will be conducted at 3 and 6 months post randomization. Different RAs will be used to complete baseline and follow-up assessments, in order to maintain blinded follow-up assessment. If possible, follow-up will be conducted in person at Bellevue Hospital Center. If necessary, follow-ups may be completed in the community. If in-person follow-up is not possible, follow-up visits may be conducted by phone. Substance use measures (Barriers to Treatment, Short Inventory of Problems, TCU Treatment Motivation Scales, The World Health Organization Quality of Life [WHOQoL Bref], Form 90-D, and Urine Drug Screen, and objective verification of pharmacotherapy through the New York Prescription Drug Monitoring Program and methadone programs where participants report receiving treatment) similar to those of the baseline assessment will be completed at follow-up, and comprehensive treatment utilization data will be collected using the Form 90-D. None of the follow up assessments are clinical assessments. All study personnel will be trained in the administration of the assessments via formal protocol training. A Training Documentation Form, endorsed by the study’s Principal Investigator, will certify the research team member’s competence to complete the measures. If a participant comes in for his or her 6-month follow-up and he or she has missed the 3-month follow-up, the RA will reconstruct the Form 90-D for the first 3-month period and complete all 6-month follow-up assessment items.

c.7. Blinding

As in almost all psychosocial treatment protocols, study participants will not be blinded. However, RAs will be blinded to treatment condition at follow-up. At the beginning of the follow-up interview, the RAs will read a brief script that informs the participant that they should not reveal their treatment assignment.

c.8. Interventions

c.8.1. Screening, Assessment and Referral. Following randomization, participants in the SAR condition will be provided with minimal scripted feedback to let them know that their assessment indicates substance dependence, and given a recommendation to seek treatment. The RA will provide these participants with an information sheet listing treatment (including both specialty treatment centers and primary care clinics that provide buprenorphine) and self-help resources in their community. The referral sheet includes names, addresses, and phone numbers of local addiction treatment agencies. Because the Bellevue Hospital Center ED does not currently screen or refer systematically, the SAR condition represents a level of care significantly higher than “treatment as usual.” Participants will also receive an informational pamphlet about drug use and its consequences, addiction, and treatment, as used in the SMART-ED study.

c.8.2. Brief Strength-Based Case Management. The structure of SBCM follows the widely accepted functions of case management—assessment, planning, linking, monitoring and advocacy [92, 93]—and the theory-driven gestalt of the strengths perspective [94]. Strengths-based principles include an emphasis on client strengths, teaching clients a method for setting and completing goals, and development of a strong working alliance [94, 95]. The emphasis on client strengths is based on the work of Bandura who found that individuals are most likely to repeat successful behaviors if they can find precedent for those behaviors in their own experiences [96-98]. The importance of relationship development, or working alliance, has repeatedly been identified as one of the most crucial elements of client success, both in therapy and case management relationships [99-101]. The importance of client-driven goal setting was established in earlier clinical trials of SBCM [94, 95, 102]. SBCM addresses barriers in four broad areas—logistical, coordinative, individually and socially mediated—articulated by Messeri in a study of linkage to medical care [103]. Case managers are expected to be intimately familiar with community resources, including substance abuse treatment, housing services, medical clinics, job banks, etc., in order to help inform client’s selections of services. Additionally, case managers will provide resources to participants such as program brochures, printed applications for social services and informational pamphlets, etc., to help facilitate linkage with care. When logistical difficulties such as transportation, childcare and identification are present, case managers make transportation arrangements or provide transportation themselves.

The six case management sessions for the proposed trial are based on those described in manuals developed by Dr. Rapp for two clinical trials, one supported by NIDA [56] and another by the CDC [70]. Each session is guided by specific objectives that promote linkage with and retention in substance abuse treatment, particularly pharmacotherapy for opioid dependence in a specialty or primary care setting. Objectives from the earlier trials will be adapted to fit the specific context of this trial, linking with and staying in treatment following an ED visit. Initiation of the relationship between client and case manager begins immediately following random assignment and termination takes place when either (1) six sessions have occurred; (2) ninety days have elapsed; or (3) clients discontinue involvement.

Session One. The first session will take place as soon as possible following patient's random assignment to the SBCM condition. If possible, this session will be completed before the participant leaves the ED. The primary goal of session one is to begin development of a relationship between case manager and client. The following objectives guide the initial one-half hour session: discussion of services available with SBCM, discussion of the events preceding the emergency department visit, initial identification of strengths, assets and abilities, identifying the client's opinion about going to substance abuse treatment and making plans for linkage to treatment (if the client has already decided to pursue substance abuse treatment) or a next meeting with the case manager (if the client has not yet decided to enter treatment). Whether the client is linking with treatment or working on other goals case managers will utilize the Linkage and Personal Goals Roadmap. The Roadmap will provide a structure for writing objectives in specific, measurable terms and identifying the strategies that will need to be implemented to accomplish objectives.

Session Two. If the client has already linked with care the case manager will engage him/her in a discussion of early treatment experiences and actual or potential barriers to continuing retention. Together the client and case manager will develop a plan for addressing these barriers. Clients who have not yet linked with care will continue to work with the case manager on the objectives that were formulated during the first session. Case managers will integrate discussions about linking into the session, helping clients to identify the way in which substance use interferes with clients' plans. Identification of client strengths enhances the case manager relationship with the client and increases clients' sense of self-efficacy in accomplishing their goals.

Sessions Three - Five. These three sessions will follow objectives similar to the first two sessions. For clients already linked with care the continuing emphasis will be on identifying potential barriers to continued retention and making plans to mitigate those barriers before they actually occur. Efforts will often involve reducing tangible barriers to treatment such as transportation, scheduling, or intake procedures. Other barriers may become apparent during this time, such as lack of family or social support or a need to preserve confidentiality. If linkage to treatment has not yet occurred, the case manager will continue to help the client to consider their immediate needs and possible barriers to linkage. Throughout these sessions the case manager will remind the client of the limited number of sessions that they have remaining to work together. This is done as part of the disengagement process and to encourage the client to make best use of the time remaining, hopefully by linking with addiction treatment in a specialty or primary care setting.

Session Six (Final session). During this meeting the client and case manager will finalize the disengagement process. For linked clients, this includes a review of the barriers overcome, a reinforcement of the client's strengths and self-identified rationale for linking to medical care, and a review of the plan for continuing in care. Clients who have not linked to care will also benefit from a review of their progress in transitioning to the community and a reiteration of the benefits of eventual linkage to treatment. At this time the case manager and client will develop a provisional outline for how to link to care if the client subsequently elects to seek treatment.

c.9. Assessment schedule. The selected assessment battery attempts to balance the value of comprehensive data against the costs of data collection in terms of staff time, feasibility of completion in the ED, financial cost, and assessment reactivity. Therefore, assessments have been limited to those that contribute directly to the objectives of the study. Estimated times for the baseline, 3-month, and 6-month assessments are 100 min., 80 min., and 80 min., respectively.

Table 1. Assessment Schedule*

Procedure / Measure	Baseline	3-M follow up	6-M follow up
Form 90-D	X	X	X
Demographics	X		

Locator form	X	X	X
Urine drug screen (UDS)	X	X	X
Texas Christian University – Treatment Motivation Assessment (TCU-TMA)	X	X	X
Barriers to Treatment (BTI)	X	X	X
WHO Quality of Life-BREF (WHOQoL Bref)	X	X	X
Short Inventory of Problems (SIP)	X	X	X
Assessment of AEs & SAEs (if spontaneously reported)	X	X	X

*Working Alliance Inventory-Short Version (WAI-SR) is completed immediately after the first SBCM session for participants assigned to SBCM.

c.10. Measures

c.10.1. Screening instrument. The logistics of screening in the ED require that the screening process be relatively brief. The screening instrument includes the Brief Information Tool (BIT), the DSM-IV Checklist and the Screening Instrument Secondary Screening Form. The BIT will collect anonymous information including English proficiency, age, gender, reason for ED visit, triage acuity level, non-prisoner status, and availability for treatment. The Screening Instrument Secondary Screening Form will provide a complete review of eligibility criteria prior to the informed consent.

c.10.2. DSM-IV substance use disorder criteria. Substance use disorder criteria will be queried by self-report using the DSM-IV [112] checklist used in several past NIDA CTN trials involving patients with opioid dependence with or without co-occurring stimulant dependence [113-115]. A recent secondary analysis in a sample of 383 stimulant-using methadone maintenance patients demonstrated that all symptoms assessed in this manner had moderate to high discrimination of drug use severity, and that the internal consistency of item sets for both opioid dependence and cocaine dependence was high (Cronbach's alphas > 0.8), supporting the use of this methodology in settings where efficiency and ease of administration is critical [116].

c.10.3. Form 90-D: Substance use and treatment participation. The Form 90, originally developed for Project MATCH, provides reliable measures of drug and alcohol use, treatment, and general functioning [117-119]. For the proposed study we will use the Form 90-D, a version of the Form 90 which has been modified to assess for all substances rather than focusing on alcohol. The Form 90-D incorporates time-line follow-back procedures [120, 121] using a calendar-based interview which yields a continuous daily record of use of each category of illicit drug. For each substance, each day of use is categorized as light, medium, or heavy use, and mode of administration (e.g., IV use) is recorded. Test-retest reliability for current (past 90 days) substance use is very good [119, 122], and concurrence with urine drug screen data is good [119]. Three modifications will be made to the standard Form 90-D. First, as in the SMART-ED study the baseline assessment the period of assessment will be limited to 30 days. Second, the actual dates of counseling and pharmacotherapy will be recorded on the calendar, to allow temporal ordering of treatment activities and substance use, necessary for Aim 5. Third, separate items will be created for methadone, buprenorphine, oral naltrexone, depot naltrexone, and overdose reversal kits containing naloxone, and the form will capture setting of all addiction treatment services received (specialty vs. primary care). It is estimated that the Form 90-D assessment will take approximately 30 minutes to complete at baseline (30 day assessment period) and approximately 45 minutes at follow-up (approximately 90 day assessment period).

c.10.4. Urine drug screens. As an objective measure of opioid use, a temperature-monitored urine sample will be obtained at baseline, the 3-month follow-up visit and the 6-month follow-up visit, and tested on site using an immunoassay for opiates, cocaine, oxycodone, methadone, propoxyphene, as well as methamphetamine, amphetamine, benzodiazepines, buprenorphine, MDMA, phencyclidine, tricyclic antidepressants, and cannabinoids. While we considered more frequent urine drug screening, we propose to defer all outcome assessments until the 3-month follow-up, as done in the SMART-ED study, in order to minimize the effects of contact, particularly in the SAR group, prior to the primary outcome assessment at 3 months. These data will not be included in subjects' medical records.

c.10.5. Objective verification of pharmacotherapy received. In order to verify self-reported use of medications for opioid dependence, two sources of information will be used. First, we will obtain dosing information from methadone and buprenorphine programs where participants report they have been treated.

Second, the New York Prescription Drug Monitoring Program will be accessed to identify all opioid prescriptions that participants fill during the follow-up period. While this does not prove that the participant actually took the medication prescribed, it allows verification of self-report.

c.10.6. Session Record Forms. Session Record Forms will be completed for each SBCM session and will capture basic information about each session. These forms will include session date, time, whether the session was interrupted, case management functions performed and whether a referral to treatment was made.

c.10.7. Non-Study Treatment Form (NTF). The NTF will be completed by RAs at approximately 1 month after the patient's admission to the ED using chart review. This form will track ED discharge diagnoses, whether the patient was admitted to the hospital and length of stay, whether the patient received any additional substance-related interventions during their ED visit, and whether the patient was discharged with any substance use medications (e.g., withdrawal medications).

c.10.8. Assessment of Motivation: The TCU-TMA. Several well-established scales exist for the assessment of motivation in substance abuse populations, including the SOCRATES [123], the URICA [124], the TREAT [125], the Readiness to Change Questionnaire [126], and the Texas Christian University-Treatment Motivation Assessment (TCU-TMA) [127], derived from the CMRS treatment motivation instrument [128]. The TCU-TMA was used in an earlier NIDA clinical trial of SBCM (Dr. Rapp, PI) [56] because of its widespread use in relevant populations including methadone maintenance patients [127, 129], probationers [130], patients in residential treatment [131], and cocaine abusers [132]; and its prediction of session attendance and treatment engagement in prior studies [129, 131, 133]. Analysis of TCU-TMA data from a pre-linkage population demonstrated that the factor structure was different than that of post-linkage populations [134, 135] . Twenty of the original 23 items from the TCU-TMA provided the best fit to the data, with factors: Problem Recognition (alpha = 0.90), Desire for Change (alpha = 0.57), Treatment Readiness (alpha = 0.82), and Treatment Reluctance (alpha = 0.69) [135]. The TCU-TMA will be administered at baseline, 3, and 6 months.

c.10.9. Working Alliance Inventory – Short Version (WAI). The 12-item Working Alliance Inventory (WAI-SR) [136] is a self-report measure based on Bordin's [137] formulation of working alliance. The WAI-SR comprises 12 Likert-scaled items that assess the extent to which the individual experiences the therapist and therapy as helpful. Similar to the original 36-item WAI, the WAI-SR consists of three subscales: the Goal subscale addresses the extent to which therapy goals are important, mutual, and capable of being accomplished; the Task subscale focuses on the participant's agreement about the steps taken to help improve the client's situation; and the Bond subscale measures mutual liking and attachment. A psychometric evaluation of the WAI-SR [136] indicated that the instrument demonstrated adequate factor structure, differentiated between Goal, Task, and Bond alliance dimensions, and correlated well with other alliance measures. Tracey and Kokotovic [138] reported strong internal consistency (Cronbach's alpha = .98) of the WAI-SR. The WAI-SR will be completed following initial SBCM session.

c.10.10. Barriers to Treatment Inventory (BTI). Participants will complete the 25-item Barriers to Treatment Inventory [139] at baseline and at 3-month follow-up. This Likert-scaled questionnaire has seven internally consistent subscales relating to Absence of Problem, Negative Social Support, Fear of Treatment, Privacy Concerns, Time Conflict, Poor Treatment Availability, and Admission Difficulty. It may be used to identify perceived barriers regardless of whether the individual has sought or engaged in treatment. We will add three items to this scale related to child-care, child custody, and child protective services involvement. The BTI has demonstrated validity across gender, ethnicity, and age [140, 141].

c.10.11. Locator Questionnaire. An electronic locator form, including home address, will be completed at baseline and updated at the 3- and 6- month follow-up visits and in-between visits, if new locator information is obtained. Data collected on the Locator Questionnaire will be used to facilitate contact with the participants during the research and follow-up. Participants will be asked to provide locator information including their contact information and the contact information of friends or relatives who can reach the participant if the participant cannot be reached directly.

c.10.12. Consequences of substance use. The drug-specific form of the Short Inventory of Problems **(SIP-D)** [142] past 3 month version, will be used to measure consequences of drug use at each time point. The SIP-D is derived from the original alcohol-specific SIP, a short (15-item) form of Drinker's Inventory of Consequences (DrInC) [143]. Psychometric evaluation of the SIP-D in a severely impaired population of patients entering substance abuse treatment yielded a single factor with Cronbach's alpha = 0.97, and strong evidence convergent and discriminant validity [142]. Although versions of the SIP exist that combine alcohol and drug

consequences [144, 145], the correlation between alcohol and drug consequences can be low [142], suggesting that it is important to assess drug consequences separately if they are of primary interest.

c.10.13. Physical, psychological, social, and environmental quality of life (WHOQoL Bref). Quality of Life will be assessed at baseline and at 3 and 6 months. At least 15 measures have been used to assess quality of life opioid dependent populations [146]. Quality of Life has consistently been found to improve following engagement in addiction treatment. Case Management addresses many different life domains that have an impact on quality of life, such as work, housing, and legal problems as well as medical, psychiatric, and dental needs; we hypothesize that people with more needs in these areas will benefit more from SBCM. For this reason we wish to use a broad measure of QoL rather than an instrument focusing narrowly on health-related QoL. Of available brief general QoL measures, The WHOQoL Bref [147] is an attractive option because it is well validated in a variety of populations including opioid dependent patients. Studies using the WHOQoL have demonstrated lower quality of life among opioid addicts than in controls [148, 149], and improvements in quality of life with opioid replacement therapy [150-152]. The WHOQoL Bref includes 26 items with 4 subscales covering the physical health, psychological, social, and environmental domains. The domain scores have good internal consistency, test-retest reliability, and discriminant validity [147].

c.11. Training, Supervision, and Fidelity Monitoring Procedures for Study Interventions

c.11.1. Training and Credentialing in SBCM

Training for SBCM. A 2-day training in SBCM will be required of research study staff who will deliver the strengths based case management. The content of the training will be based on existing 2-day training formats, modified as needed for the specific content of the SBCM sessions described in the SBCM manuals. This training will consist of a basic introduction to the SBCM model, role-play exercises, complete review of the study treatment manual, and practice sessions of the study interventions.

Pilot Delivery of Interventions. Upon completion of the basic training, interventionists conducting the brief interventions in the ED will be required to complete at least 2 practice cases (totaling no less than 5 SBCM sessions) with consenting pilot/training patients, and receive satisfactory fidelity ratings in order to be certified. If the pilot cases are judged by the supervisor to be satisfactory in quality, the data from the pilot participants will be included in the main trial.

c.11.2. Treatment Fidelity for SBCM.

Supervision of Interventionists. All SBCM sessions will be digitally audiotaped if possible. Participants may opt out of audiotaping. These files could theoretically be identifiable by voice quality or details of the conversation. The digital audio recordings will be transferred from the audio recorder to a password protected, HIPAA compliant secure storage drive. Recordings will be identified by participant number, session number, date, and research study member. The recordings will only be accessible to study team members including the SBCM supervisor. Supervision for SBCM will be provided by collaborator Richard Rapp, PhD., of Wright Stated University. Dr. Rapp is the person who developed the SBCM model of case management. His role on the project is limited to training and supervision/fidelity monitoring of staff who are conducting the SBCM intervention. Audiotapes of all interventionists will be reviewed and scored by Dr. Rapp (using the same Adherence Scale used by the fidelity monitor-see below) and reviewed in a biweekly telephone supervision session. Research study members will also have back-up available through the existing clinical hierarchy at the Bellevue Hospital Center ED.

Quality Control of SBCM. Following completion of the trial, a randomly selected sample of 20% of sessions completed during the trial will be coded using the SBCM Adherence Scale as a formal measure of treatment fidelity during the trial. The digital audio recordings will be destroyed upon completion of the quality control of SBCM.

SBCM Adherence Scale. This scale includes 5 Likert-scaled items, 5 in each of 3 dimensions of the SBCM model. The “Strengths” dimension rates the extent to which the case manager elicits and affirms client strengths, and incorporates these strengths into assessment and the planning of goals. The “individual-driven” dimension supports participant autonomy and choice in the determination of goals and courses of action in working with the case manager. The “relationship” dimension rates the extent to which the case manager establishes a strong alliance with the participant and demonstrates respect and empathy for their concerns.

c.12. Statistical Methods

An extensive set of preliminary analyses are planned but are not fully described because of page restrictions. In addition to the assessment of the distributional properties of key measures at baseline and

follow-up, we will evaluate the nature and pattern of missing data and assess treatment group equivalency at baseline on primary substance use measures and patient characteristics that are central to study aims. Three areas of preliminary analyses are highlighted below given their importance for the achievement of study aims. All primary analyses will be based upon an intent-to-treat (ITT) approach.

c.12.1. Self-selection and Attrition. The DSM-IV will be administered as a measure of substance use prior to informed consent, a procedure that facilitates comparing (1) substance use patterns of eligible and ineligible participants, and (2) eligible prospects who do and do not elect to participate in the study. Contingent on the scale of measurement of the comparison variable, unprotected t-tests and Chi Squares will be done to compare these groups. Two strategies will be used to examine the impact of attrition on study internal validity, and both strategies will employ hierarchical linear modeling (HLM) with binary outcomes depicting attrition status (yes/no) jointly at three and six-months (Bernoulli function). First, we will examine attrition by group assignment. Here, the HLM will identify both the main effect of group assignment on later attrition as well as the potential for a group-by-time attrition effect. Second, group equivalency on factors potentially predictive of future treatment seeking will be evaluated with one-way ANOVA's using scales from the BTI, TCU-TMA, and WHO-QoL scales as dependent measures. Third, using a lagged HLM we will examine how, if at all, substance use and general functioning at baseline and three-month follow-up predicts attrition at the three and six-month follow-up.

c.12.2. Convergent validity of self-report of substance use and urine toxicology. The veracity of self-reported illicit drug use will be examined by determining the concordance between positive urine toxicology screens and Form 90-D self-reported use at baseline, and at the 3 and 6 month follow-ups. Concordance will be determined both in categorical terms (agreement on the presence or absence of substance use) via Chi Square with kappa correction and, for continuous daily counts of substance use, Intraclass correlation.

c.12.3. Convergent validity of pharmacotherapy initiation and engagement data. The initiation and engagement in treatment and pharmacotherapy for opioid dependence will be determined using three methods. The Form 90-D interview will collect retrospective report of frequency of counseling sessions, inpatient/residential treatment, ambulatory and hospital-based detoxification (items 9, 10, 11, 12, 13, 23, and 24) and pharmacotherapy for opioid dependence. Days use of one (or more) of four medications will be summed to indicate days of pharmacotherapy for opioid dependence: methadone, buprenorphine, P.O. naltrexone, and depot naltrexone (one injection of depot naltrexone will count as 30 days of pharmacotherapy). These events will be recorded on the day-by-day calendar to allow for the investigation of temporal associations between medication and substance use. As described in Section c.10.5, two objective methods will be used to verify self-reported use of medications for opioid dependence: methadone and buprenorphine clinic dosing records and New York State's Prescription Monitoring Program. Days of pharmacotherapy will be estimated from these records based on days dispensed or administered, and concordance between the objective records and self-report will be computed. Discrepancies will be reconciled prior to conducting primary analyses (self-reported days of pharmacotherapy will be capped at the number of days of medication that was dispensed or administered).

c.12.4. Study Aim 1. The *a priori* pairwise contrast (SBCM vs. SAR) will investigate the main effect of study group assignment on initiation of addiction treatment and engagement in pharmacotherapy for opioid dependence. Following Rapp et al. [56], "Initiation" will be defined as a dichotomous outcome (yes/no), and will be considered to have occurred if patients report any substance abuse counseling sessions (excluding SBCM) from the time of the baseline assessment up to the day before the three-month interview. Using the same timeframe as "initiation," "engagement" will be defined as the number days of medication use for opioid dependence, based on self-report verified by clinic dosing logs and Prescription Drug Monitoring Program records. Generalized linear modeling (GLM) will be used to test the planned contrasts, with group assignment as the between-subject factor (df = 1), and baseline measures of days substance use, number of lifetime treatment episodes for substance misuse, and readiness for change used as covariates. A logit link function will be used with the dichotomous outcome measure, initiation, while a linear distribution will be assumed with the continuous engagement outcome measure. Given the definitional overlap between the two primary dependent measures and our planned contrasts we will apply a Bonferroni correction of $\alpha = .05/2 = .025$ (two-tailed) in rejecting the null hypothesis.

c.12.5. Study Aim 2. Pairwise between-group contrasts analogous to those in Aim 1 are planned for Aim 2, with the difference that post-randomization opioid use is the outcome. The primary analysis will be based on a dichotomous measure of "successful outcome," analogous to the outcomes used in a recent NIDA

CTN trial of buprenorphine with and without opioid drug counseling [153], and in the NIAAA COMBINE trial [82]. For the present study "successful outcome" will be defined as 1) 3-month urine negative for opioids (opiates, oxycodone, methadone, buprenorphine, or propoxyphene) unless prescribed for opioid dependence, and 2) no more than two days of self-reported opioid use in the 4 weeks prior to the 3-month evaluation. Here, we will perform logistic regressions in which 3-month successful outcome (yes/no) is the dependent measure and baseline covariates are entered in step 1. Baseline days of opioid use will be used as a covariate as well as baseline readiness for change and number of lifetime treatment episodes for substance misuse. Treatment group will be dummy coded and entered in step 2 of the analysis. Secondary analysis will separately examine urine drug screen data and three-month self-reported opioid use, here defined as the total number of days of opioid use in the 30-day window before the 3-month interview (Form 90). Additional parallel analyses will be conducted for other drugs of abuse, IV drug use, and six-month substance use defined using the same strategies described above.

c.12.6. Study Aim 3. To test the effects of SBCM on other important life-functioning areas we will contrast SBCM with SAR (both groups combined) on each of the 4 subscales of the WHOQoL Bref. Baseline scores for each of these measures will be used as covariates when investigating its corresponding three-month value. GLM-based application of ANCOVA will be used to test the main effect of SBCM and alpha for each test will be set at .0125 (.05/4). Two sets of secondary analyses are planned. First we will investigate the extent, if any, that improvement in life-functioning areas (3-months) has a prognostic main effect on 6-month substance use reductions. Second, using longitudinal HLM we will investigate the trajectories of change in quality of life from baseline to the 6-month follow-up.

c.12.7. Study Aim 4. We predict that (1) SBCM will have a larger effect (relative to SAR) on initiation and engagement in participants with higher levels of environmental instability at baseline. Definitions of initiation and engagement will parallel the definitions used in Aim 1. Environmental instability at baseline will be defined by summing five items in the Form 90-D interview, with higher scores reflecting more instability: number of days homeless, days living with others (not paying rent), days living in a halfway house, days incarcerated, and days not paid for work (all past 30 days). GLM will be used to test the predicted interactions. Covariates in these analyses will include baseline measures of days of opioid use and number of lifetime treatment episodes for substance misuse. Main effect terms representing treatment group and the selected participant attribute and the interaction term (group x attribute) will be entered simultaneously. For the environmental instability moderator we predict that the slope between instability and outcome will be significant and positive within the SBCM group while this parameter estimate within the SAR condition will be non-significant (ordinal interaction).

c.12.8. Study Aim 5. This aim will identify the relative importance of study treatment effects and later initiation of/engagement in non-study treatment in predicting substance use reductions, i.e., does initiation or engagement mediate the relationship between study group assignment and outcome? Analyses will focus on 3-month opioid use outcome although 6-month outcomes will be investigated to ascertain the stability of findings over time. Three-month substance use will be defined as the total number of days of opioid use in the 30-day window before the 3-month (Form 90-D). To provide for non-overlapping data initiation and engagement will be defined the same way as in all other aims (two measures), but this time only considering post-randomization months 1 and 2. Baseline days of opioid use as well as number of lifetime treatment episodes for substance misuse will be used as covariates. Aim 4 findings may result in one additional covariate, environmental instability. Using GLM, we plan to assess the mediating effect of initiation and engagement (separately for each measure) in two steps: in step 1, the main effect of treatment assignment (df = 2) and covariate effects will be tested against a protected alpha of .05/2 = .025. In step 2 the main effect of initiation or engagement will be entered into the model, with the prediction that this term will eliminate the main effect of treatment assignment. Parallel and confirmatory analyses will be done using "successful outcome" and 3-month opioid drug screen results as dependent measures. Following the same stepwise strategy used in the GLM, separate logistic regression models will be used to determine if initiation and engagement measures account for the dichotomous outcomes over and above the benefits from the SCBM intervention. Several additional secondary analyses are planned to investigate, in detail, the temporal relationship between daily substance use, use of medications for opioid dependence, and treatment group assignment. As an example, we will use a hierarchical generalized linear model (HGLM: Bernoulli sampling model and a logit link function) to *prospectively* determine if the initiation of

medications for opioid dependence predicts, in a lagged design, reduction in opioid use, and whether the strength of this relationship varies by treatment condition, e.g., cross-level interactions [154].

c.13. Statistical power

Power analyses were calculated for Aims 1 and 2 as these objectives involve between-group contrasts pertaining to the most important outcome measures: linkage to addiction treatment and opioid use. In our planned pairwise contrasts for both Aims 1 and 2 we anticipate an attrition rate of 15% leading to a reduced N of 127 per cell, and base our calculations on a desired power of .80. For Aim 1, effect size estimates are based on reported effects for case management relative to treatment as usual (TAU) or another less intensive treatment. In reviewing 10 studies investigating the effectiveness of case management versus TAU in facilitating later treatment engagement, the Cochrane group reported an effect size of d = .43 favoring case management, with a larger effect (d = .70) for SBCM and for studies in which the treatment was manualized (d = .56) [68]. Assuming a two-tailed test, df = 1, our power projections suggest that the proposed cell sizes after attrition and Bonferroni correction (α = .025) are sufficiently powered to detect a differential effect as small as d = .32. Regarding drug use (Aim 2), studies contrasting the effectiveness of case management with that of treatment as usual or lower intensity treatments have yielded heterogeneous results. While the overall effect relative to TAU was small (d = .12), larger effects on drug use were found in three studies with above average linkage effects (d = .33) [68]. In the single most relevant trial, a large (n = 711) study with an opioid dependent sample, case management yielded an intermediate (d = .23) reduction in drug use relative to psychoeducation and drug counseling [68]. We have calculated that with a two-tailed test, df = 1, α = .05, our proposed cell sizes will have sufficient power to detect effects as small as d = .20 to reject the null hypothesis, an effect size that falls midway between small and moderate [155].

PROTECTION OF HUMAN SUBJECTS

1. RISKS TO HUMAN SUBJECTS

1.1. Human Subjects Involvement and Characteristics.

The protocol will enroll approximately 400 women and men, age 18 or greater, with opioid dependence, recruited from the Bellevue Hospital Center Emergency Department. Participants will be recruited between approximately January 2016 and December 2019. Participants will be screened and assessed in the ED using procedures based closely on those used in our recently completed CTN-0047 trial. Participants identified as having opioid dependence will be randomly assigned (150 per group) to receive 1) up to 6 sessions of Strength-Based Case Management (SBCM) based on the model previously implemented by Rapp et al. [56]; or 2) screening, assessment and referral alone (SAR). Follow-up assessments will be completed at 3 and 6 months, by RAs who are blinded to treatment condition.

The treatment sessions will all be scheduled within a 90-day period for SBCM. Including screening and follow-up visits, the total duration of participant involvement will be approximately 6 months. Total time of contact during these 6 months is estimated at 5-10 hrs. Participants will meet the aforementioned inclusion and exclusion criteria. As noted in section c.2.3, the study will not recruit prisoners. If a subject becomes incarcerated during the study, treatment and follow-up procedures may be continued in accordance with IRB and OHRP approvals.

1.1.1. Research sites

Screening, consent, baseline assessments, and the initial intervention session will be performed at Bellevue Hospital Center Hospital. SBCM sessions 2-6 and follow-up assessments may be conducted at Bellevue Hospital Center, at NYULMC, or in the community. Should the initial intervention not occur on the date of consent and baseline, the session may take place as soon as possible and at locations noted for sessions 2-6 and follow-up assessments. Supervision of the SBCM intervention will be performed remotely by Dr. Richard Rapp at Wright State University.

1.2. Sources of Materials.

Urine samples will be obtained from participants. Data will be collected through use of interviews, questionnaires, and data collected from treatment providers and the New York Prescription Drug Monitoring Program. These data will include measures of substance use and substance use disorder diagnoses, consequences of substance use, treatment participation, motivation, therapeutic alliance, barriers to treatment, demographics, contact information, and quality of life. Case management sessions will be audiotaped for fidelity monitoring purposes. Participants may opt out of audio-recording.

These materials and data will be obtained specifically for research purposes, and the link to subject identifiers will be kept only on a separate enrollment log and in the REDCap database, accessible only to project staff.

1.3. Potential Risks

1.3.1. Risks of psychosocial treatments

There are no known specific risks to any of the psychosocial treatments employed in this study. Non-specific risks of psychosocial treatments include discomfort with sharing personal information, and the risk of therapist misconduct. These risks are judged to be very minor.

As a consequence of study participation, subjects may receive information concerning the severity of their substance use problems, and their participation implies that they may have an opioid use disorder. This risk is judged to be minimal, since patients are already being screened for drug and alcohol use as part of standard of care treatment. It is very unlikely that qualifying participants are unaware that they have significant problems with opioid use. In addition, the consent form explicitly states that the study is testing an intervention linking patients to treatment for substance use disorder. Therefore, patients are unlikely to agree to participate if they do not already think that they have or may have an opioid use disorder.

1.3.2. Risks of assessment procedures
There are no known psychological risks associated with the questionnaires used in the study, all of which have been used extensively in clinical populations. It is possible that discussing substance use and consequences may cause emotional discomfort in some participants. To minimize such discomfort, the following steps will be taken. The consent form will fully inform the participants about the nature of the information to be disclosed in the protocol, and the participants will be informed in the consent form that they can refuse to answer any questions or withdraw from the study at any time. Participants will be informed that all information is confidential, and the steps taken to guard confidentiality, as well as the limits to confidentiality, will be described. One of the investigators of the project will be available to meet with any participant who becomes distressed about any aspect of the protocol and wishes to discuss this.

1.3.3. Risks to confidentiality and potential legal consequences.
Records which identify subjects and the consent form signed by subjects may be inspected by the NYU Institutional Review Board. The purpose for the review of this information would be to encourage and assess compliance with GCP requirements and to document the integrity of the trial progress. De-identified information may also be reviewed by NIH, the sponsor of this study. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. No information will be shared with outside parties during objective verification of pharmacotherapy received. Because illicit substance use and addiction are stigmatized, there are possible social and legal consequences to breach of confidentiality concerning this information. The results of this research project may be presented at meetings or in publications. However, the identity of individual subjects will not be disclosed in those presentations.

1.3.4. Risks and benefits of alternative treatments.
There is no standard emergency department treatment for opioid dependence in the Bellevue Hospital Center ED. Patients who are noted to have opioid dependence are sometimes referred to social work to be referred for treatment. It is possible for ED physicians with a CSAT waiver to initiate treatment with buprenorphine, but this happens rarely. Because of the ethical problem of participants receiving a lower level of care due to participation in the study (particularly those in the SAR group), participation in the study will not preclude the participants' receiving whatever clinical care would otherwise be provided by the ED. Therefore such interventions are not actually "alternative" treatments but rather additional treatments that study participants may or may not receive independent of study participation.

2. ADEQUACY OF PROTECTION AGAINST RISKS

2.1. Recruitment and Informed Consent

2.1.1. Recruitment
Participants will be recruited from the Bellevue Hospital Center ED.

2.1.2. Informed consent process and document.
2.1.2.1 Bellevue ED staff will introduce the ED patient to study staff.
2.1.2.2 Using a brief IRB-approved script, study staff will request the patient's verbal consent, to complete the prescreen assessment.
2.1.2.3 The RA will collect anonymous information from potentially eligible patients including English proficiency, age, gender, reason for ED visit, triage level, non-prisoner status, days of opioid use in the past 30 days, and availability for treatment (See form entitled "Brief Information Tool") in order to determine potential eligibility and collect data on representativeness of the study sample.
2.1.2.4 A research study member will administer the DSM-IV Checklist.
2.1.2.5 ED patients who meet DSM-IV inclusion criteria (endorsement of three or more opioid dependence criteria on the DSM-IV Checklist.) will be further screened for eligibility by the RA using the Screening Instrument Secondary Screening Form. Those who are interested and eligible will then undergo the written informed consent process.

Trained research staff will conduct the informed consent process in private locations as noted below. Interested patients will be provided with an informed consent form including all pertinent details of the study including description of the following: the assessment interview and questionnaires; the follow-up interviews; description of experimental treatment; risks and benefits of study procedures; alternatives to participation in the study; confidentiality; emergency treatment and compensation for injury; payment for participation; a statement that patients will be informed of any new findings affecting the risks or benefits of the study; a statement that participation is voluntary and that the patient may withdraw at any time; and information about whom to contact with questions or in case of emergency. The consent form will also include assurances of confidentiality and a statement that participation is entirely voluntary, that the decision to participate will in no way influence other aspects of the patient's treatment or involvement in the main trial, and that the participant is free to withdraw participation at any time. Patients indicate their consent to participate in the study by signing and returning the informed consent form. This form provides documentation that written informed consent has been obtained. A copy of the signed informed consent form will be given to the study participant.

2.2. Protection Against Risk

2.2.1. Management of risk due to study treatments

The psychosocial treatments employed in this study are minimal risk. Risks will be minimized by thorough training, supervision, and monitoring of those providing the interventions, as described in Section 3.c.11 of the Research Plan.

2.2.2. Minimization of risk to confidentiality and privacy

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. No identifying information will be disclosed in reports, publications or presentations. Confidentiality will be maintained in accordance with all applicable federal regulations and/or state law and regulations.

All project staff will be thoroughly trained in issues relating to confidentiality. Data will be entered into "Research Electronic Data Capture" (REDCap) which is maintained by the NYU CTSI. The link between participant identifiers and participant study ID will be maintained only in REDCap and on a password-protected electronic storage drive. REDCap was designed specifically to protect patient privacy and confidentiality while assisting investigators in conducting clinical research. System-level and application-level security features include: SSL encryption of internet traffic (e.g. https pages); Hosting in the secure data centers with centralized nightly backup; Sanitization of database inputs against scripting or SQL injection attacks; Fine-grained control over user rights; Detailed audit trails; Record-locking; De-identification functions for data export. At the conclusion of this study de-identified data will be downloaded and the project will be deleted off of REDCap. Confidentiality of hard copy (paper) research materials will be ensured by storing the research materials in locked cabinets. Material will be available only to project staff, and only as needed. Participants will be identified in CRFs by a unique identification code. Documents containing participants' identities (consent forms, source documents) will be stored in a separate locked cabinet. Audio files of sessions will be stored on a password protected, HIPAA compliant secure server. Published reports will be based on group data; no individual data will be reported. No information will be shared with outside parties during objective verification of pharmacotherapy received.

As a further protection to confidentiality, the principal investigator has obtained a federal Certificate of Confidentiality (CoC) from the Department of Health and Human Services (DHHS), protecting participants against disclosure of sensitive information (e.g., drug use). The NIH office that issues the CoC will be advised of changes in the CoC application information. With this Certificate, the investigators cannot be forced (for example by court order or subpoena) to disclose research information that may identify individual patients in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes. DHHS ensures confidentiality of requested data. Data and study records (including consent forms, locator forms, source documents, session audio files, and CRFs) will be kept a minimum of 3 years after all final reports have been

submitted to NIDA. After that they will be destroyed. A de-identified database will be retained in electronic form as a permanent record of the study.

Bellevue ED staff will introduce the potential participants to study staff at a time when they are deemed to be medically and psychiatrically stable, when their medical care will not be disrupted or delayed, and when the adequate privacy exists.

The interviewer will ensure a private setting for the interview and will ask the patient's comfort with the privacy prior to interview initiation. Screening, informed consent, assessment, and initial SBCM sessions may be completed in private rooms or other private treatment areas (e.g., ophthalmology room). If the patient is moved, the staff member will notify patient's doctor or nurse so that medical staff is aware of patient location. If the patient is unable to move easily, either due to lack of mobility or proximity to certain medical machines, the staff member will consult with a nurse as to whether it is possible to move participant. If it is not possible, the staff member will explore possibility with nurse as to whether patients surrounding the participant can be moved to afford the participant more privacy.

If the patient feels uncomfortable with or is emotionally disturbed by any portion of the interview, s/he may elect to not answer portions of the interview or may end the interview without loss of the compensation for their time.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS

3.1. Potential benefits to participants

Participants in both groups will receive care above treatment-as-usual. All participants will receive substance use screening, assessment and information on local substance use treatment programs. Participants assigned to SBCM will additionally receive up to 6 SBCM sessions with a trained case manager who can provide additional resources and support to the participant. Referral to treatment and case management are evidence-based treatments in other contexts. As stated in section c.2.3, incarcerated participants will be clearly informed in advance that participation in the research will have no effect on parole, nor will it confer any advantages or amenities beyond the potential benefits stated at the time of informed consent.

3.2. Potential benefits to others.

Knowledge gained through this study may aid the development of more effective treatments for individuals with opioid dependence and other addictive disorders.

3.3. Risk-benefit assessment

Risks to individual participants appear to be outweighed by the likely benefits of study participation and the potential benefits to others.

4. COMPENSATION TO PARTICIPANTS

Participants will receive reimbursement for research assessments as follows: Screening and Baseline assessment: $50, 3-month follow-up: $75, 6-month follow-up: $75. Participants completing all of the assessments would therefore receive a total of $200. Upon request, participants randomized to SBCM will be given a roundtrip Metro Card for each case management visit. Upon request, both groups (SBCM and SAR) will be given a roundtrip Metro Card for the 3 and 6 month follow-up interviews. If a participant is found to be incarcerated at time of follow-up, the participant will be compensated the agreed upon amount as approved by local IRB and/or collaborating correctional facilities.

5. COSTS TO PARTICIPANTS

None.

6. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

There is an urgent need to develop more effective methods to help people who suffer from opioid dependence. The knowledge gained through this study could help establish effective ways of facilitating engagement in addiction treatment by patients with opioid dependence who present for treatment in medical EDs.

7. DATA AND SAFETY MONITORING PLAN

7.1. General Considerations

The risks of the interventions used in this study are minimal. However, the population under study is at high risk for serious adverse events unrelated to study participation. The data and safety monitoring plan is therefore designed 1) to monitor study progress, including recruitment, retention, data quality, and adherence to the protocol; and 2) to ensure that the risks of study-related procedures are carefully monitored, and that all reportable adverse events are systematically evaluated.

7.2. Institutional Review Board (IRB)

All study procedures will be approved by the NYU IRB prior to beginning the study.

7.3. Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will be established comprising the Principal Investigator and Co-investigators, the Protocol Manager, and an external physician reviewer who is not otherwise affiliated with the study and does not report directly or indirectly to the PI. This committee will meet at least twice per year to review data quality, recruitment and retention, and to review all serious or clinically significant adverse events. In addition, the committee will review safety data, including AEs/SAEs and reportable new information following any serious adverse event that appears to be study related. Patterns of adverse events as well as individual events may indicate the need for operational changes or protocol modifications, or termination of the study. Because this study involves a very low-risk psychosocial intervention, there are no predefined stopping rules for the study. DSMC reports will be forwarded to the IRB with the annual continuing review.

7.4. Procedures for Monitoring and Reporting Adverse Events.

AEs will be reported in accordance with federal law, NIH policies, and NYUSOM IRB policies to the NYU IRB. In addition, information on adverse events will be captured as follows.

7.4.1. Data Collection for Adverse Events and Serious Adverse Events

7.4.1.1. Adverse Events. For the purpose of this study, the following events will not be reported as AEs:

- Grade 1 (mild) unrelated event.
- Grade 2 (moderate) unrelated event. This would typically include physical events such as headache, cold, etc. that were considered unrelated to study participation.
- Substance Use Events, including:
    - Worsening of drug use
    - Need for higher level of care
    - Signs and symptoms of withdrawal
    - Drug craving
    - Medical events that are directly related to substance use

Events that are severe, life threatening, or result in death will be recorded as AEs or SAEs as appropriate and documented in the study progress note and in the data system.

7.4.1.2. Serious Adverse Events. For the purpose of this study, the following events will not be reported as SAEs:

- Admission to a hospital or freestanding residential facility for drug detoxification or drug treatment.
- Admission to a hospital/surgery center for preplanned/elective surgeries;
- Admission to a hospital for scheduled labor and delivery;

• Inpatient hospital admission for a medical event (i.e. gallbladder surgery, pneumonia, substance related).

7.4.1.3 Reportable New Information. For the purpose of this study, the following information will be reported to the NYU SoM IRB within 5 business days:

- Information that indicates new or increased risk, or a safety issue.
- Any harm experienced by a subject or another individual that, in the opinion of the investigator, is unexpected and at least probably related to the research procedures.
- Non-compliance with federal regulations governing the research or within the requirements or an allegation of such non-compliance.
- Audit, inspection or inquiry by a federal agency.
- Written reports of study monitors.
- Failure to follow the protocol due to the action or inaction of the investigator or research staff.
- Breach of confidentiality.
- Unreviewed change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
- Complaint of a subject that cannot be resolved by the research team.
- Premature suspension or termination of the research by the sponsor, investigator or institution.

8. CLINICALTRIALS.GOV REQUIREMENTS

This application includes a trial which requires registration in ClinicalTrials.gov. The signature on the application of the Authorized Organizational Representative assures compliance for the registration of any such trial.

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